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EXAMINER	
KOSAR, AARON J	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,521	LENTZ ET AL.	
	Examiner	Art Unit	
	AARON J. KOSAR	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33 and 43-71* is/are pending in the application.

4a) Of the above claim(s) *16-33 and 43-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 58-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed January 23, 2009 to claims 1, 3, 4, and 9-12 have been entered. Claims 23-26 and 34-42 have been cancelled. Claims 52-71 have been added. Claims 1-22, 27-33, and 43-71 are pending in the current application, of which claims 1-15 and 58-71 are being considered on their merits. Claims 16-22, 27-33, and 43-51 remain withdrawn from consideration at this time. New claims 52-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions there being no allowable generic or linking claim. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Objections

Claims 60 and 65 are objected to because of the following informalities:

The claims recite "C4-C12" which appears to be similar to other disclosed/claimed ranges and might be an inadvertent typographical error either of the range "C2-C14" (as recited in claim 10) or of the disclosed subgenus range excluding C11, "C4 to C10 or C12"(see specification, page 13). Claims 60 and 65 are being treated as claimed, as "C4 to C12"; however, if another range is intended, the claims should so indicate. Clarification is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 58-71 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 58, 62, and 67 are indefinite because it is unclear if the "sample" of the preamble is the same as the "sample" of step (a). This deficiency also renders claims 2-6, 12, 13, 61, 66, and 71 unclear, because these additional claims depend from the indefinite parent claims and also recite a "sample" and it is unclear which sample is intended by the claims. Clarification is required.

Claim 1, step (c) recites the phrase "activity of Factor Xa or thrombin correlates with clotting factor activity in the sample" which is unclear because it is unclear what "activity" of Factor Xa or of clotting factor is intended and thus it is unclear how the activity of Factor Xa or thrombin "correlates with" or how the skilled artisan would arrive at a conclusion of clotting factor activity or clotting factor activity in the sample. Claims 3, 4, 58, 62, and 67 suffer similar deficiencies and are thus included in this ground of rejection. Clarification is required.

Claims 1, 58, 62, and 67 recite the limitation "the mixture of (a)" in step (b). There is insufficient antecedent basis for this limitation in the claim, because the claims do not recite a mixture. Clarification is required.

Claim 3 is rejected because the term "Protein C resistance" is unclear because it is unclear as to what object(s) against which Activated Protein C has "resistance". Clarification is required.

Because claims 2-4, 6-15, 59-61, 63-66, 70, and 71 depend from indefinite claims 1, 3, 58, 62, and 67, and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-9, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Gempeler *et al* (2001, WO 01/44493 A2; IDS) as evidenced by Hürter *et al* (1970, *Pediatrics*, 46(2), pp. 259-266) and Boos *et al* (2003, US 2003/0080056 A1; reference A).

Gempeler anticipates the claims by teaching a body fluid coagulation-potential assay comprising a body fluid, including plasma; contacting with phospholipids, calcium ($CaCl_2$), and an activator (e.g. RVV-V); incubating at 37 °C; and detecting activity as indicated by optical measurements of clotting (e.g. Example 1, pages 15-16). Gempeler further teaches a heparinised sample (LMWH, heparin: page 16, lines 32 and 35; claim 24) and assayed for an activity of factor Xa and thrombin (i.e. clotting time: page 16, example 2, lines 32-33; figure 7). Although Gempeler does not teach the presence/degree thereof of a particular phospholipid, as evidenced by Hürter, plasma intrinsically comprises a degree of phospholipids, including phosphatidylserine (PS) and phosphatidyl-ethanolamine (PE) among others (Hürter, table II). Although Gempeler or Hürter do not explicitly teach that plasma contains "soluble" phospholipids or phospholipids that are soluble in a blood or plasma sample, plasma contains

soluble phospholipids, as evidenced by Boos which teaches that "the lipids of the blood plasma (cholesterol, triglycerides and phospholipids) are by their nature water-insoluble and are present in soluble form in the aqueous medium of the blood due to the combination with specific proteins." (page 2, paragraph [0027]).

Claims 1, 2, 5, 7, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Triplett *et al* (1998, US 5,705,198 A; IDS) as evidenced by Hürter *et al* (1970, *Pediatrics*, 46(2), pp. 259-266) and Boos *et al* (2003, US 2003/0080056 A1; reference A).

Triplett anticipates the claims by teaching a method of evaluating clotting activity, including evaluating lupus anticoagulant (LA) activity (e.g. abstract; columns 7-8, examples 4 and 5). Triplett teaches combining a plasma sample; soluble phospholipids, including phosphatidylserine and phosphatidylethanolamine obtainable by extraction or commercially-available; a contact activator; and calcium (chloride), including the incubation thereof to activate thrombin/detect thrombin activity (abstract; summary; column 5, paragraph 3,4; examples 4 and 5). Triplett further teaches contacting with normal human plasma and detecting clot formation (e.g. Example 2). Although Triplett does not explicitly teach the presence/degree thereof of a particular phospholipid in a plasma sample, as evidenced by Hürter, plasma also intrinsically comprises a degree of phospholipids, including phosphatidylserine (PS) and phosphatidylethanolamine (PE) (table II). Also, as evidenced by Boos, plasma phospholipids are soluble, by teaching "the lipids of the blood plasma (cholesterol, triglycerides and phospholipids) are by their nature water-insoluble and are present in soluble form in the aqueous medium of the blood due to the combination with specific proteins." (page 2, paragraph [0027]).

Response to Arguments

Applicant has argued that the phospholipids will form membrane-like structures or other aggregated phases at the concentrations required for a clotting assay and that synthetic phospholipids means insoluble synthetic membranes (Remarks page 18, paragraph 2). Applicant's arguments have been fully considered but they are not persuasive.

Regarding Applicant's argument that the phospholipids of Gempeler are aggregated at the assay concentration and thus cannot be the phospholipids of the instant claims (Remarks page 19, lines 31-32 and through column 20, line 4), this is not persuasive, because the claims do not require that the phospholipid be added to the sample which is not naturally present in the sample. Claim 1 does not require, for example, that the phospholipid added in step (a) be purified to any degree. Also the plasma sample of Gempeler intrinsically comprises soluble phosphates, which for the reasons of record as evidenced by Hürter, plasma contains the species phosphatidylserine (PS) and phosphatidylethanolamine (PE). According to instant claim 9, PS and PE are species of "phospholipid", and thus to the extent the prior art teaches these species, it meets the claim limitation of a phospholipid. Still further, the claims do not require a preferred/intended degree of aggregation or of solubility in the sample and a preferred or intended embodiment from the specification regarding a preferred/intended degree of aggregation or of solubility in the sample is not read into the claims. It is noted that the language of the claim is open ("A method comprising"), so including additional components, e.g. proteins that are naturally bound to the phospholipids, in the mixture of step (a) is not precluded by the claim. It is further noted that only claims 11 and 58-71 limit the amount of phospholipid added in step (a).

Applicant has arguments regarding the cited references to Bloor, Marcus, Tanford (Remarks, page 18-19 and footnotes 1-3) are acknowledged; however, the arguments thereof are not persuasive because Boos teaches that the phospholipids are soluble and because the claims do not require the conditions or compositions referenced therein. For example, the instant claims:

(i) do not require that the solubility be measured in the conditions of Bloor ((Remarks, page 18, Bloor, footnote (1)) or Tanford (Remarks, page 18, Tanford, footnote (3)), which, for example, Tanford teaches aqueous solubility and critical micelle concentration (CMC) measured at 25°C (Tanford, page 100); and

(ii) only claims 10, 60, 65, 67, and 70 limit the phospholipid fatty acid acylation pattern to phosphatidylserine acylated by C2 to C14 or C4 to C10 fatty acids. The remaining claims do not preclude a "C16 or longer" acylation (Remarks, page 18, Marcus, footnote (2)).

Applicant's arguments that the composition of Gempeler will form aggregates at the concentration required for a clotting assay (Remarks page 18, lines 13-18) are not persuasive, because only claims 11, 58-61, 63, 64, 68 , and 69 require a phospholipid concentration and these claims are not included in the ground of rejection by Gempeler.

Regarding Applicant's argument that the specification defines synthetic phospholipids to mean insoluble synthetic membranes (Reply, page 18, lines 16-18), this is not persuasive, because the claims do not recite "synthetic phospholipids", "synthetic membranes" or "insoluble phospholipids", only that the phospholipids be "soluble" in some way.

Regarding Applicant's arguments that Triplett does not teach a soluble phospholipid (Reply, page 18, lines 16-18, page 19, lines 5-12), this is not persuasive, because Triplett is not so limited to the preferred phospholipids cited therein (Triplett column 5; see also Remarks, page

21), but merely requires that the phospholipid be a phospholipid (e.g. Triplett, claims 6, 15) or comprise phosphatidylethanolamine (PE) or phosphatidylserine (PS) (e.g. Triplett, claim 16). Furthermore, as evidenced by Boos, PE and PS are inherently soluble in blood plasma when complexed with proteins (Boos, paragraph [0027]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I. GEMPELER

Claims 1-3, 5-9, 13 and 14 are rejected under 35 U.S.C. 103(a), as unpatentable over Gempeler *et al* (2001, WO 01/44493 A2; IDS), in view of Hürter *et al* (1970, *Pediatrics*, 46(2), pp. 259-266) and Boos *et al* (2003, US 2003/0080056 A1; reference A).

Gempeler teaches a body fluid coagulation-potential assay comprising a body fluid, including plasma; contacting with phospholipids, calcium ($CaCl_2$), and an activator (e.g. RVV-

V); incubating at 37 °C; and detecting activity as indicated by optical measurements of clotting (e.g. Example 1, pages 15-16). Gempeler further teaches a heparinised sample (LMWH, heparin: page 16, lines 32 and 35; claim 24) and assayed for an activity of factor Xa and thrombin (i.e. clotting time: page 16, example 2, lines 32-33; figure 7). Gempeler also teaches combining with activated protein C or endogenous protein C and activators thereof (e.g. thrombin/thrombo-modulin), assaying for factor V resistance, and providing other assays (page 16, line 35 through example 2, page 17). Also, Gempeler teaches the interrelation of the enzymes/factors in the clotting cascade, including the dependence upon activated protein C (APC) of protein S and the relation/further interdependence upon thrombin, prothrombin, Ca^{+2}, phospholipid, Factor Va, Factor Xa, etc. (figures 1, 4). Gempeler further beneficially teaches providing a dried form by teaching providing of a lyophilized preparation (e.g. page 9, paragraph 1).

Gempeler does not explicitly teach a working example providing a lupus sample in the method. Gempeler also does not teach comparing with a standard.

Hürter teaches that plasma intrinsically comprises a degree of phospholipids, including phosphatidylserine (PS) and phosphatidyl-ethanolamine (PE) among others (Hürter, table II).

Boos teaches that plasma intrinsically comprises soluble phospholipids, by teaching that "the lipids of the blood plasma (cholesterol, triglycerides and phospholipids) are by their nature water-insoluble and are present in soluble form in the aqueous medium of the blood due to the combination with specific proteins." (page 2, paragraph [0027]).

Regarding claim 2, it would have been *prima facie* obvious to have provided a lupus sample, because Gempeler teaches that in assay method one may provide a number of equivalent samples including "human plasma,…human whole blood (or animal blood or plasma)" (page 10,

lines 23-25) and further that the method may assess "whole blood or plasma suspected of the presence of an antibody against one or more blood coagulation components, e.g. lupus coagulant."(page 11, lines 8-10).

Although Gempeler does not explicitly teach the presence/degree thereof of a particular phospholipid in a plasma sample, in light of Hürter, plasma intrinsically comprises a degree of phospholipids, including phosphatidylserine (PS) and phosphatidyl-ethanolamine (PE) among others (Hürter, table II).

Although Gempeler or Hürter do not explicitly teach that plasma contains "soluble" phospholipids or phospholipids that are soluble in a blood or plasma sample, ~~as evidenced by~~ in light of Boos, plasma contains soluble phospholipids, by Boos's teaching that "the lipids of the blood plasma (cholesterol, triglycerides and phospholipids) are by their nature water-insoluble and are present in soluble form in the aqueous medium of the blood due to the combination with specific proteins." (page 2, paragraph [0027]).

Also, although Gempeler does not teach comparing the detected thrombin activity with a standard, as instantly claimed (claim 14), this may be done manually or as a mental step and thus is still embraced by the teachings of Gempeler.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gempeler in light of Hürter and Boos as applied to claims 1-3, 5-9, 13, and 14 above, and further in view of Matschiner (1996, US 5,525,478 A; IDS).

Gempeler, Hürter, and Boos, are relied upon as applied above.

Gempeler, Hürter, and Boos do not teach combining with Protein S-depleted plasma in the method.

Matschiner teaches that protein S functions as a blood coagulation component (i.e. essential blood coagulation components involved in the normal down-regulation of blood coagulation)(column 1, lines 56-58). Matschiner also teaches that functional abnormalities, including protein S-deficiencies, are common to 4-5% of the global population as protein S- or protein C-deficiency and that such persons "should be regularly monitored" (column 1, line 62 through column 2, line 9).

The selection of a Protein S-deficient plasma would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that protein S functions in blood clotting/coagulating, is of similar chemical nature as the sample of Gempeler (i.e. a blood/plasma sample), and because Matschiner teaches that protein S-deficient samples should be monitored regularly. A holding of obviousness over the cited claims is therefore clearly required.

Claim 9 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gempeler in view of Hürter and Boos as applied to claims 1-3, 5-9, 13, and 14 above, and further in view Gorman *et al* (2002, US 6,451,610 B1; reference B) and Zhai *et al* (2002, *Biochem.*, 41(17), pages 5675-5684; IDS 7/31/06).

Gempeler, Hürter, and Boos, are relied upon as applied above.

Gempeler, Hürter, and Boos do not teach providing the species of phospholipid, and contact activators, as in claim 9 and 15.

Gorman teaches that sources of phospholipids which function in clotting cascade assays include the phospholipids comprising phosphatidyl choline, phosphatidyl serine, ethanolamine, and other neutral lipids (Gorman column 2, lines 48-50). Although Gorman does not expressly

teach phosphatidic acid, since the instant claims are open language and permit other components and since phosphatidic acid is a shared core ("phosphatidyl") structure of the phospholipids of Gorman, the species taught by Gorman still embrace providing in the method a composition consisting essentially of or comprising phosphatidic acid. Gorman also teaches that contact activators include the species of kaolin, ellagic acid, celite, glass beads, and colloidal silica (column 2, lines 46-48).

Zhai teaches that soluble lipids of phosphatidylserine, including 1,2-Dicaproyl-snglycero-3-phospho-L-serine (C6PS), and phosphatidylhomoserine, including the species of 1,2-Dicaproyl-sn-glycero-3-phospho-D-homoserine (C6P(h)S), enhance cofactor activity in the clotting pathway assays (page 5676, lines 8-12 and "Materials"; figure 1).

Regarding claim 9, the selection of a phospholipid or phosphatidic acid would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that phospholipids are cofactors/enhancers in clotting assays and that the above species are equivalent sources of phospholipid for clotting assays (Gorman, column 1, line 43; column 2, lines 48-50). A holding of obviousness over the cited claims is therefore clearly required.

Regarding claim 15, the selection of a contact activator species of kaolin, ellagic acid, celite, glass beads, and colloidal silica would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that species are recognized equivalents, as contact activators, in the art of clotting assays (Gorman, column 1, line 43; column 2, lines 48-50). A holding of obviousness over the cited claims is therefore clearly required.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gempeler in view of Hürter and Boos as applied to claims 1-3, 5-9, 13, and 14 above, and further in view of Opalsky (2002, US 6,438,498 B1; reference C).

Gempeler, Hurter, and Boos are relied upon as above.

Gempeler, Hurter, and Boos do not teach the many contact activators as recited in claim 15, namely clay and diatomaceous earth.

Opalsky teaches that coagulation inducers (contact activators) include "celite, kaolin, diatomaceous earth, clay, silicon dioxide, ellagic acid, natural thromboplastin, recombinant thromboplastin, phospholipid, and mixtures thereof." (column 11, lines 31-33).

The selection of a contact activator species, including clay and diatomaceous earth, would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that species are recognized equivalents, as contact activators (coagulation inducers), in the art of clotting assays (column 11, lines 31-33). A holding of obviousness over the cited claims is therefore clearly required.

Claims 11, 12, 58, 59, and 61 are rejected under 35 U.S.C. 103(a) as unpatentable over Gempeler *et al* in view of Hürter *et al* and Boos *et al* as applied over claims 1-3, 5-9, 13, and 14 above, and further in view of Sigma (2000, *Sigma Catalogue*, 2000/2001, pages 782-791.).

Gempeler, Hürter, and Boos are relied upon as presented above.

Gempeler, Hürter, and Boos do not expressly teach a phospholipid or a species thereof in plasma nor does Gempeler teach that the phospholipids are soluble. Gempeler Hürter, and Boos also do not teach a concentration or particular degree of hydration (dryness or "dry form") of phospholipids.

Sigma teaches concentration/hydration of phospholipids and that the degree of moisture/dilution is a result effective variable by teaching that compositions may decompose at ambient temperature in solution, wherein the phospholipids are commercially available in dry form, including as lyophilized powders stored under argon (e.g. Sigma, "phosphatidylethanolamine", page 788; "phosphatidylserine", page 791).

Regarding claims 11, 12, and 58, 59, and 61, where Gempeler does not teach a particular phospholipid having a particular concentration, it would have been obvious to have adjusted the concentration or degree of hydration, because Sigma teaches that the degree of moisture/dilution (i.e. hydration/concentration) is a result effective variable (i.e. effects decomposition/storage, see above and e.g. Sigma, "phosphatidylethanolamine", page 788; "phosphatidylserine", page 791). Thus, it would have been obvious to one skilled in the art at the time of invention to determine the optimum and operable conditions as instantly claimed (i.e. the degree of dryness/moisture/hydration/concentration of reagents provided and the optimal concentrations, ratios, and proportions of the component reagents respective to the amount of water/hydration), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. Thus one seeking to provide a composition would have appreciated and have been motivated to provide the composition in dried form and reconstitute to a desired volume, because one would not want the composition to have decomposed. One would have had a reasonable expectation of success, because success merely requires providing the compositions in a desired amount which is routine in the art.

Claims 10, 60, 62, 65, 67, and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gempeler in view of Hürter and Boos, as applied to claims 1-3, 5-9, 13, and 14 above, and further in view of Majumder *et al* (2002, *Biophys. J.*, 277(33), pages 29765-29733; IDS 7/31/2006).

Gempeler, Hürter, and Boos are relied upon as presented above.

Gempeler, Hürter, and Boos do not teach a soluble phospholipid having a C2-C14, or C4-C10 fatty acid or detection using quasi-elastic light scattering (QELS).

Majumder teaches that the C6 phospholipid, 1,2-dicaproyl-*sn*-glycero-3-phospho-L-serine (C6PS) was known and commercially available (page 29766, Methods, 1st paragraph). Majumder also teaches that the degree of aggregation of the C6PS is measured by quasi-elastic light scattering (QELS) (page 29766, Methods, 2nd paragraph) and that C6PS produces thrombin from meizothrombin/soluble prothrombinase complex in the activation of prothrombin to thrombin (page 29765, abstract). Majumder also teaches C6PS added in a range below the critical micelle concentration (CMC), at a concentration of 30-400μM (page 29765, abstract).

The selection of a C2-C14, C4-C12, or C4-C10 phospholipid would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that C6PS and the phospholipids of Gempeler in light of Hurter and Boos share a common core structure of a phosphatidyl serine, and recognizing that C6PS phospholipid functions to provide thrombin activation (page 29766, Methods, 2nd paragraph). A holding of obviousness over the cited claims is therefore clearly required.

Claims 10, 60, and 62-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gempeler in view of Hürter, Boos, and Sigma (2000, *Sigma Catalogue*, 2000/2001, pages 782-

791.) as applied to claims 1-3, 5-9, 11-14, 58, 59, and 61 above, and further in view of Majumder *et al* (2002, *Biophys. J.*, 277(33), pages 29765-29733; IDS 7/31/2006).

Gempeler, Hürter, Boos, Sigma, and Majumder are relied upon as applied above.

Gempeler, Hürter, Boos, and Sigma do not teach a soluble phospholipid having a C2-C14, or C4-C10 fatty acid or detection using quasi-elastic light scattering (QELS).

Majumder teaches that the C6 phospholipid, 1,2-dicaproyl-*sn*-glycero-3-phospho-L-serine (C6PS) was known and commercially available (page 29766, Methods, 1st paragraph). Majumder also teaches that the degree of aggregation of the C6PS is measured by quasi-elastic light scattering (QELS) (page 29766, Methods, 2nd paragraph) and that C6PS produces thrombin from meizothrombin/soluble prothrombinase complex in the activation of prothrombin to thrombin (page 29765, abstract). Majumder also teaches C6PS added in a range below the critical micelle concentration (CMC), at a concentration of 30-400μM (page 29765, abstract).

The selection of a C2-C14, C4-C12, or C4-C10 phospholipid would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that C6PS and the phospholipids of Gempeler in light of Hurter and Boos share a common core structure of a phosphatidyl serine, and recognizing that C6PS phospholipid functions to provide thrombin activation (Majumder, page 29766, Methods, 2nd paragraph). A holding of obviousness over the cited claims is therefore clearly required.

II. TRIPLETT

Claims 1-3, 5, 7-9, and 12-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Triplett *et al* (1998, US 5,705,198 A; IDS), in view of Hürter *et al* (1970, *Pediatrics*, 46(2), pp. 259-266) and Boos *et al* (2003, US 2003/0080056 A1; reference A).

Triplett teaches a method of evaluating clotting activity, including evaluating lupus anticoagulant (LA) activity (abstract; columns 7-8, examples 4 and 5). Triplett teaches combining a plasma sample; soluble phospholipids, including phosphatidylserine and phosphatidylethanolamine obtainable by extraction or commercially-available; a contact activator; and calcium (chloride), including the incubation thereof to activate thrombin/detect thrombin activity (abstract; summary; column 5, paragraphs 3, 4; examples 4 and 5). Triplett further teaches contacting with normal human plasma and detecting clot formation (Example 2) and beneficially teaches a dry form, by teaching reconstitution (e.g. column 5).

Triplett does not expressly teach the presence/degree thereof of a phospholipid or a phospholipid species thereof in a plasma sample. Triplett does not expressly teach water-insolubility or a soluble form in a plasma sample. Triplett also does not teach comparing to a standard.

Hürter teaches that plasma intrinsically comprises a degree of phospholipids, including phosphatidylserine (PS) and phosphatidyl-ethanolamine (PE) among others (Hürter, table II).

Boos teaches that plasma intrinsically comprises soluble phospholipids, by teaching that "the lipids of the blood plasma (cholesterol, triglycerides and phospholipids) are by their nature water-insoluble and are present in soluble form in the aqueous medium of the blood due to the combination with specific proteins." (page 2, paragraph [0027]).

Although Triplett does not explicitly teach the presence/degree thereof of a particular phospholipid in a plasma sample, in light of Hürter, plasma intrinsically comprises a degree of phospholipids, including phosphatidylserine (PS) and phosphatidyl-ethanolamine (PE) among others (Hürter, table II). Although Triplett or Hürter do not explicitly teach that plasma contains

"soluble" phospholipids or phospholipids that are soluble in a blood or plasma sample, in light of Boos, plasma contains soluble phospholipids, by Boos's teaching that "the lipids of the blood plasma (cholesterol, triglycerides and phospholipids) are by their nature water-insoluble and are present in soluble form in the aqueous medium of the blood due to the combination with specific proteins." (page 2, paragraph [0027]).

Also, Although Triplett does not teach comparing the detected thrombin activity with a standard, as instantly claimed (claim 14), this may be done manually or as a mental step and thus is still embraced by the teachings of Triplett.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gempeler in view of Hürter and Boos as applied to claims 1-3, 5, 7-9, 12-15 above, and further in view of Matschiner (1996, US 5,525,478 A; IDS).

Triplett, Hürter, and Boos, are relied upon as applied above.

Triplett, Hürter, and Boos do not teach combining with Protein S-depleted plasma in the method.

Matschiner teaches that protein S functions as a blood coagulation component (i.e. essential blood coagulation components involved in the normal down-regulation of blood coagulation)(column 1, lines 56-58). Matschiner also teaches that functional abnormalities, including protein S-deficiencies, are common to 4-5% of the global population as protein S- or protein C-deficiency and that such persons "should be regularly monitored" (column 1, line 62 through column 2, line 9).

The selection of a Protein S-deficient plasma would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that protein S

functions in blood clotting/coagulating, is of similar chemical nature as the sample of Triplett (i.e. a blood/plasma sample), and because Matschiner teaches that protein S-deficient samples should be monitored regularly. A holding of obviousness over the cited claims is therefore clearly required.

Claim 9 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Triplett in view of Hürter and Boos as applied to claims 1-3, 5, 7-9, and 12-15 above, and further in view Gorman *et al* (2002, US 6,451,610 B1; reference B) and Zhai *et al* (2002, *Biochem.*, 41(17), pages 5675-5684; IDS 7/31/06).

Triplett, Hürter, and Boos, are relied upon as applied above.

Triplett, Hürter, and Boos do not teach providing the species of phospholipid, and contact activators, as in claim 9 and 15.

Gorman teaches that sources of phospholipids which function in clotting cascade assays include the phospholipids comprising phosphatidyl choline, phosphatidyl serine, ethanolamine, and other neutral lipids (Gorman column 2, lines 48-50). Although Gorman does not expressly teach phosphatidic acid, since the instant claims are open language and permit other components and since phosphatidic acid is a shared core ("phosphatidyl") structure of the phospholipids of Gorman, the species taught by Gorman still embrace providing in the method a composition consisting essentially of or comprising phosphatidic acid. Gorman also teaches that contact activators include the species of kaolin, ellagic acid, celite, glass beads, and colloidal silica (column 2, lines 46-48).

Zhai teaches that soluble lipids of phosphatidylserine, including 1,2-Dicaproyl-snglycero-3-phospho-L-serine (C6PS), and phosphatidylhomoserine, including the species of 1,2-

Dicaproyl-sn-glycero-3-phospho-D-homoserine (C6P(h)S), enhance cofactor activity in the clotting pathway assays (page 5676, lines 8-12 and "Materials"; figure 1).

Regarding claim 9, the selection of a phospholipid or phosphatidic acid would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that phospholipids are cofactors/enhancers in clotting assays and that the above phospholipid species are equivalent sources of phospholipid for clotting assays (Gorman, column 1, line 43; column 2, lines 48-50) as the phospholipids of Triplett. A holding of obviousness over the cited claims is therefore clearly required.

Regarding claim 15, the selection of a contact activator species of kaolin, ellagic acid, celite, glass beads, and colloidal silica would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that species are recognized equivalents to the prothrombin/clotting activator of Triplett, as contact activators, and are known in the art of clotting assays (Gorman, column 1, line 43; column 2, lines 48-50; Triplett, abstract). A holding of obviousness over the cited claims is therefore clearly required.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Triplett in view of Hürter and Boos as applied to claims 1-3, 5, 7-9, and 12-15 above, and further in view of Opalsky (2002, US 6,438,498 B1; reference C).

Triplett, Hurter, and Boos are relied upon as above.

Triplett, Hurter, Boos do not teach the many contact activators as recited in claim 15, namely clay and diatomaceous earth.

Opalsky teaches that coagulation inducers (contact activators) include "celite, kaolin, diatomaceous earth, clay, silicon dioxide, ellagic acid, natural thromboplastin, recombinant thromboplastin, phospholipid, and mixtures thereof." (column 11, lines 31-33).

The selection of a contact activator species, including clay and diatomaceous earth, would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that species are recognized equivalents, as contact activators (coagulation inducers), in the art of clotting assays (column 11, lines 31-33). A holding of obviousness over the cited claims is therefore clearly required.

Claims 10, 62, 65, 67, and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Triplett in view of Hürter and Boos, as applied to claims 1, 2, 5, 7-9, and 12-15 above, and further in view of Majumder *et al* (2002, *Biophys. J.*, 277(33), pages 29765-29733; IDS 7/31/2006).

Triplett, Hürter, and Boos are relied upon as presented above.

Triplett, Hürter, and Boos do not teach a soluble phospholipid having a C2-C14, or C4-C10 fatty acid or detection using quasi-elastic light scattering (QELS).

Majumder teaches that the C6 phospholipid, 1,2-dicaproyl-*sn*-glycero-3-phospho-L-serine (C6PS) was known and commercially available (page 29766, Methods, 1st paragraph). Majumder also teaches that the degree of aggregation of the C6PS is measured by quasi-elastic light scattering (QELS) (page 29766, Methods, 2nd paragraph) and that C6PS produces thrombin from meizothrombin/soluble prothrombinase complex in the activation of prothrombin to thrombin (page 29765, abstract). Majumder also teaches C6PS added in a range below the critical micelle concentration (CMC), at a concentration of 30-400μM (page 29765, abstract).

The selection of a C2-C14, C4-C12, or C4-C10 phospholipid would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that C6PS and the phospholipids of Triplett in light of Hurter and Boos share a common core structure of a phosphatidyl serine, and recognizing that C6PS phospholipid functions to provide thrombin activation (Majumder, page 29766, Methods, 2nd paragraph). A holding of obviousness over the cited claims is therefore clearly required.

It would have been obvious to have used QELS to determine the state of aggregation of the phospholipid in the method of Gempeler, because Majumder teaches that QELS is known to measure the state of protein aggregation, including that of C6PS phospholipids in clotting/prothrombin activation assays. One would have been motivated to have used QELS because one providing a phospholipid of Majumder to the method of Gempeler would recognize that Majumder teaches that it is important to known whether reactions are "due to individual molecules...or to an aggregate form" (page 29767, left column, last paragraph and portion spanning right column) and because Majumder further teaches that by varying the concentration of the phospholipid (e.g. C6PS) that one may determine the concentration effecting aggregation micelle formation (CMC) (figures 1 and 2, insets). The reasonable expectation of success comes from Majumder and the Gempeler each being directed to the same field of endeavor, clotting/prothrombin activation assays, and because Majumder teaching that teaching that QELS functions in these assays.

Claims 11, 58, 59, and 61 are rejected under 35 U.S.C. 103(a), as unpatentable over Triplett *et al* in view of Hürter *et al* and Boos *et al* as applied to claims 1-3, 5, 7-9, and 12-15 above, and in further view of Sigma (2000, *Sigma Catalogue*, 2000/2001, pages 782-791.).

Triplett, Hürter, and Boos are relied upon as presented above.

Also, Triplett does not teach a concentration or particular degree of hydration (dryness or "dry form") of phospholipids.

Triplett does not expressly teach a phospholipid or a species thereof in plasma nor does Triplett teach that the phospholipids are soluble. Triplett also does not teach a concentration or particular degree of hydration (dryness or "dry form") of phospholipids.

Sigma teaches concentration/hydration of phospholipids and that the degree of moisture/dilution is a result effective variable by teaching that compositions may decompose at ambient temperature in solution, wherein the phospholipids are commercially available in dry form, including as lyophilized powders stored under argon (e.g. Sigma, "phosphatidylethanolamine", page 788; "phosphatidylserine", page 791). Sigma teaches that the degree of moisture/dilution (i.e. hydration/concentration) is a result effective variable by teaching dry compositions and that moisture/solutions effect decomposition/storage.

The selection of a degree of dryness, hydration, or dilution would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that providing a dried form and reconstituting/diluting to a desired volume/concentration would effect the decomposition of the materials. A holding of obviousness over the cited claims is therefore clearly required.

Claims 10 and 60, 62-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Triplett in view of Hürter, Boos, and Sigma as applied to claims 11, 58, 59, and 61 above, and further in view of Majumder *et al* (2002, *Biophys. J.*, 277(33), pages 29765-29733; IDS 7/31/2006).

Triplett, Hürter, Boos, and Sigma are relied upon as applied above.

Triplett, Hürter, Boos, and Sigma do not teach a soluble phospholipid having a C2-C14, or C4-C10 fatty acid or detection using quasi-elastic light scattering (QELS).

Majumder teaches that the C6 phospholipid, 1,2-dicaproyl-*sn*-glycero-3-phospho-L-serine (C6PS) was known and commercially available (page 29766, Methods, 1st paragraph). Majumder also teaches that the degree of aggregation of the C6PS is measured by quasi-elastic light scattering (QELS) (page 29766, Methods, 2nd paragraph) and that C6PS produces thrombin from meizothrombin/soluble prothrombinase complex in the activation of prothrombin to thrombin (page 29765, abstract). Majumder also teaches C6PS added in a range below the critical micelle concentration (CMC), at a concentration of 30-400μM (page 29765, abstract).

The selection of a C2-C14, C4-C12, or C4-C10 phospholipid would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that C6PS and the phospholipids of Triplett in light of Hurter and Boos share a common core structure of a phosphatidyl serine, and recognizing that C6PS phospholipid functions to provide thrombin activation (Majumder, page 29766, Methods, 2nd paragraph). A holding of obviousness over the cited claims is therefore clearly required.

It would have been obvious to have used QELS to determine the state of aggregation of the phospholipid in the method of Triplett, because Majumder teaches that QELS is known to measure the state of protein aggregation, including that of C6PS phospholipids in clotting/prothrombin activation assays. One would have been motivated to have used QELS because one providing a phospholipid of Majumder to the method of Triplett would recognize that Majumder teaches that it is important to known whether reactions are "due to individual

molecules...or to an aggregate form" (page 29767, left column, last paragraph and portion spanning right column) and because Majumder further teaches that by varying the concentration of the phospholipid (e.g. C6PS) that one may determine the concentration effecting aggregation micelle formation (CMC) (figures 1 and 2, insets). The reasonable expectation of success comes from Majumder and the Triplett each being directed to the same field of endeavor, clotting/prothrombin activation assays, and because Majumder teaching that teaching that QELS functions in these assays.

III. TANS

Claims 1, 3-5, 7, 9, 11-15, 58, 62, and 63 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tans *et al* (1991, *J. Biological Chemistry,* 266 (32), pages 21864-21873.)

Tans teaches defibrinated normal human plasma, adding kaolin (a contact activator) and calcium ($CaCl_2$), and incubating at 37ºC (e.g. page 21869; methods; figure 7, page 21873). Tans teaches assaying for prothrombin activation via prothrombin activation products, including observing thrombin as the major product (page 21869, paragraph1). The composition contains a degree of meizothrombin, wherein "meizothrombin is able to activate protein C with about 75% of the activity of thrombin" (page 21864, paragraph1). Tans also teaches contacting a prothrombin sample with a 10μM phosphatidylserine-containing (PS-containing) phospholipid (50μM total phospholipid), calcium ($CaCl_2$), and a contact activator (e.g. *E. carnitus* venom); incubation at 37ºC; and quantitative analysis of thrombin (assay 1)(e.g. Methods, paragraph 1 ("Proteins") and paragraph 8 ("Quantitative analysis"), pages 21865-21866; figure 7). As each of

the components are obtained/purified from plasma isolates, each of the purified compositions are thus broadly and reasonably interpreted as embracing Protein S depleted plasma. Tans also teaches treatment with heparin (e.g. Figure 4; page 21868, line 19). The phospholipid of Tans is broadly interpreted as "contains no detectable aggregates", because claim 62 does not require that the phospholipid have an undetectable aggregation in any combined sample, only that the phospholipid itself in some way and under some condition be below the detection threshold of a quasi-elastic light scattering (QELS) technique.

Tans does not explicitly teach that the sample contains soluble phospholipid.

Although Tans does not explicitly recite a soluble phospholipid, the selection of a soluble phospholipid in the sample would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that one would adjust the concentration of the phospholipid by reconstitution as taught by Tans (page 21865, "Lipid Preparations") and further recognizing that the dilution/concentration obtained would have a molarity (page 21865, "Proteins") and thus may broadly be interpreted as having a degree of solubility. A holding of obviousness over the cited claims is therefore clearly required.

Claims 10, 60, 65, and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tans *et al* (1991, *J. Biological Chemistry,* 266 (32), pages 21864-21873) as applied to claims 1, 3-5, 7, 9, 11-15, 58, 62, and 63 above, and further in view of Majumder *et al* (2002, *Biophys. J.*, 277(33), pages 29765-29733; IDS 7/31/2006).

Tans is relied upon as provided above.

Tans does not teach measuring the composition with QELS or a composition comprising a C12-C14 fatty acid phospholipid.

Majumder teaches that the C6 phospholipid 1,2-dicaproyl-*sn*-glycero-3-phospho-L-serine (C6PS) was known and commercially available (page 29766, Methods, 1st paragraph). Majumder also teaches that the degree of aggregation of the C6PS is measured by quasi-elastic light scattering (QELS) (page 29766, Methods, 2nd paragraph) and that C6PS produces thrombin from meizothrombin/soluble prothrombinase complex in the activation of prothrombin to thrombin (page 29765, abstract). C6PS is also added in a range below the critical micelle concentration (CMC), at 30-400μM (page 29765, abstract).

It would have been obvious to have used a soluble, C4-C12 phospholipid, because Majumder teaches that C6PS, a soluble phosphatidylserine (PS) phospholipid was known, because Tans merely requires that the composition be a "phospholipid", though egg yolk and cephalin are beneficial/preferred species of phospholipid (e.g. page 21866, "Results", paragraph 1, line 15). One would have been motivated to have used another phospholipid, for example, C6PS or other C4-C12 phospholipid of Tans because the compounds of Tans and Mujamder share a common core phospholipid structure and would have had a reasonable expectation that the similar compositions used in or added to the method would have similar functioning/utility in promoting thrombin activation/coagulation as the function/utility of the phospholipids disclosed by Tans.

It would have been obvious to have used QELS to determine the state of aggregation of the phospholipid in the method of Tans, because Majumder teaches that QELS is known to measure the state of protein aggregation, including that of C6PS phospholipids in clotting/prothrombin activation assays. One would have been motivated to have used QELS because one providing a phospholipid of Majumder to the method of Tans would recognize that

Majumder teaches that it is important to known whether reactions are "due to individual molecules...or to an aggregate form" (page 29767, left column, last paragraph and portion spanning right column) and because Majumder further teaches that by varying the concentration of the phospholipid (e.g. C6PS) that one may determine the concentration effecting aggregation micelle formation (CMC) (figures 1 and 2, insets). The reasonable expectation of success comes from Majumder and the Tans each being directed to the same field of endeavor, clotting/prothrombin activation assays, and because Majumder teaching that teaching that QELS functions in these assays.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 9 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tans as applied to claims 1, 3-5, 7, 9, 11-15, 58, 62, and 63 above, and further in view of Gorman *et al* (2002, US 6,451,610 B1; reference B) and Zhai *et al* (2002, *Biochem.*, 41(17), pages 5675-5684; IDS 7/31/06).

Tans is relied upon as applied above and in general teaches phospholipids, including egg yolk PC, DOPC, DOPE, bovine brain PS, and "phospholipid" (page 21864, footnote 2; page 21865, "Materials"; page 21868) contact activators (coagulation initiators), including Russell's viper venom, *E. carinatus* venom, and kaolin (page 21865, "Materials", lines 1,2, and 4 and "Methods"; page 21869, line 22).

Tans does not teach providing all of the species of phospholipid, and contact activators, as in claim 9 and 15.

Gorman teaches that sources of phospholipids which function in clotting cascade assays include the phospholipids comprising phosphatidyl choline, phosphatidyl serine, ethanolamine, and other neutral lipids (Gorman column 2, lines 48-50). Although Gorman does not expressly teach phosphatidic acid, since the instant claims are open language and permit other components and since phosphatidic acid is a shared core ("phosphatidyl") structure of the phospholipids of Gorman, the species taught by Gorman still embrace providing in the method a composition consisting essentially of or comprising phosphatidic acid. Gorman also teaches that contact activators include the species of kaolin, ellagic acid, celite, glass beads, and colloidal silica (column 2, lines 46-48).

Zhai teaches that soluble lipids of phosphatidylserine, including 1,2-Dicaproyl-snglycero-3-phospho-L-serine (C6PS), and phosphatidylhomoserine, including the species of 1,2-Dicaproyl-sn-glycero-3-phospho-D-homoserine (C6P(h)S), enhance cofactor activity in the clotting pathway assays (page 5676, lines 8-12 and "Materials"; figure 1).

Regarding claim 9, the selection of a phospholipid or phosphatidic acid would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that phospholipids are cofactors/enhancers in clotting assays and that the above phospholipid species are equivalent sources of phospholipid for clotting assays (Gorman, column 1, line 43; column 2, lines 48-50) as the phospholipids for the thrombin activation/clotting assay of Tans. A holding of obviousness over the cited claims is therefore clearly required.

Regarding claim 15, the selection of a contact activator species of kaolin, ellagic acid, celite, glass beads, and colloidal silica would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that species of contact activator are

recognized equivalents to the contact activator/clotting initiator of Tans, as contact activators, and are known in the art of clotting assays (Gorman, column 1, line 43; column 2, lines 48-50; Tans, abstract). A holding of obviousness over the cited claims is therefore clearly required.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tans as applied to claims 1, 3-5, 7, 9, 11-15, 58, 62, and 63 above, and further in view of Opalsky (2002, US 6,438,498 B1; reference C).

Tans is relied upon as above.

Tans does not teach the many contact activators as recited in claim 15, including celite, kaolin, diatomaceous earth, clay, silica, and ellagic acid.

Opalsky teaches that coagulation inducers (contact activators) include "celite, kaolin, diatomaceous earth, clay, silicon dioxide, ellagic acid, natural thromboplastin, recombinant thromboplastin, phospholipid, and mixtures thereof." (column 11, lines 31-33).

The selection of a contact activator species, including celite, kaolin, diatomaceous earth, clay, silica, and ellagic acid, would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that species are recognized equivalents, as contact activators (coagulation inducers), in the art of clotting assays (Opalsky, column 11, lines 31-33). A holding of obviousness over the cited claims is therefore clearly required.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Response to Arguments

Applicant's arguments with respect to claim 1-15 and 58-71 regarding the teachings Gempeler or Triplett or Tans or the new claims, with respect to the claims being drawn to a

blood- or plasma-soluble phospholipid (Remarks: page 22; "vesicles", page 23; no detectable aggregates" by Q.E.L.S., page 24), have been considered but are not persuasive in view of the new ground(s) of rejection as further applied in light of Boos and and/or in view of Majumder, Matschiner, Zhai, Opalsky, and/or, Gorman, as applied above.

Conclusion

Applicant's amendment necessitated new ground(s) of rejection presented in this Office action; however, since new grounds of rejection have also been presented, accordingly, **THIS ACTION IS MADE NON-FINAL**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AARON J. KOSAR whose telephone number is (571)270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday,EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Aaron J Kosar/
Examiner, Art Unit 1651

/Lora E Barnhart/
Primary Examiner, Art Unit 1651